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10/520,014	03/06/2006	Siegfried Ansorge	013183.00044	9468

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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/520,014	ANSORGE ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-11,17,20,25,28,30 and 39-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-11,17,20,25,28,30 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/03/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II and the species phebestin in the reply filed on 9/11/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Upon further consideration, the restriction requirement between groups I-III is withdrawn. The election of species requirement is still deemed proper.

2. Claims 1-7, 9-11, 17, 20, 25, 28, 30 and 39-43 are pending. Claims 1-4, 6, 7, 9-11, 17, 20, 25, 28, 30 and 39-43 read on the elected species phebestin.

Claim Objections

3. Claims 1-5 and 17 are objected to because of the following informalities: Treg in claim 1 should be written regulatory T cells. Appropriate correction is required.

4. Claims 2, 3, and 41-43 are objected to because of the following informalities: phosphates should be spelled phosphonates. Appropriate correction is required.

5. Claim 7 is objected to because of the following informalities: IDDM should be written insulin dependent diabetes mellitus. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7, 9-11, 17, 20, 25, 28, 30 and 39-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

8. The claims are drawn to alanyl aminopeptidase inhibitors and methods of increasing TGF-β1 expression and treating and/or preventing autoimmune and inflammatory conditions. The proposed inhibitors include β-amino thiols, α-amino phosphinic acids and their esters and salts, α-amino phosphonats, α-amino boronic acids, α-amino aldehydes, hydroxamates of α-amino acids, N-phenyl phthalimides, N-phenyl homophthalimides, α-ketoamides, thalidomide derivatives, and 3-amino-2-oxo-4-phenylbutanoic acid amides. These recitations do not describe a complete or partial structure sufficient to demonstrate possession of the claimed genus of alanyl aminopeptidase inhibitors. Does every compound comprising an α-ketoamide moiety for example have the claimed activity? What is the specific relationship between the structure of these compounds and their ability to inhibit alanyl aminopeptidase and further to influence TGF-β1 expression and treat autoimmune diseases? What method or assay is available to test the activity of this broad range of compounds?

9. The claims are further drawn to specific compounds D-Phe-γ[PO(OH)-CH_2]-Phe-Phe, PAQ-22, RB3014 and MR 387. However, the structures of these compounds are not disclosed nor are they known in the prior art. The specification discloses only the following complete

structures: actinonin, leuhistin, phebestin, amastatin, bestatin, probestin, and arphamenin. Of these compounds, only phebestin is shown to influence TGF-β1 expression. The specification does not provide a structure/function relationship for alanyl aminopeptidase inhibitors in general or a structure/function relationship between the disclosed compounds and their ability to modulate TGF-β1 expression and/or treat autoimmune and inflammatory conditions. Because of the chemical diversity of the disclosed species, the reported activity of phebestin is not representative of the entire claimed genus of alanyl aminopeptidase inhibitors.

10. The specification does not disclose compounds that inhibit enzymes that are similar to alanyl aminopeptidase. Which enzymes are similar in specificity to alanyl aminopeptidase? What are the distinguishing structural characteristics of these enzymes? How does one quantitate similarity? What is the relationship between the structure of a compound and its ability to inhibit all enzymes that are similar to alanyl aminopeptidase? How are these compounds identified?

11. Finally, the specification does the complete or partial structure of a peptide fragment of pathogenic autoantigens or synthetic analog and/or specific antigenic component of pathogenic microorganisms that would be useful for supplementing the alanyl aminopeptidase inhibitors in therapy. The relationship between the structure of such compounds and their claimed activity is not reported nor is a method for isolation.

12. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

13. With the exception of phebestin, the skilled artisan cannot envision the detailed chemical structure of an alanyl aminopeptidase inhibitor that is also capable of increasing TGF-β1 expression. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

14. Therefore, only phebestin, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

15. Claims 1-7, 9-11, 17, 20, 25, 28, 30 and 39-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of phebestin to upregulate TGF-β1 and to treat lupus and arthritis, does not reasonably provide enablement for all other alanyl aminopeptidase inhibitors or for the treatment and/or prevention of all other autoimmune disorders, hay fever, allergies, asthma or graft versus host disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make or use the invention commensurate in scope with these claims. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) the nature of the invention

16. The invention is drawn to alanyl aminopeptidase inhibitors. Methods for upregulating TGF-β1, and treating and/or preventing autoimmune disorders, hay fever, allergies, asthma and graft versus host disease are also claimed.

(2) the state of the prior art

17. Ansorge *et al.* (WO 01/89569 cited on Information Disclosure Statement received 10/3/2006) teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, leuhistin, phebestin, amastatin, probestin, β-amino thiols, α-amino phosphinic acids, and α-amino phoshinic acid derivatives (see claim 10). The compositions are disclosed as being useful for the treatment of autoimmune diseases and chronic diseases with an inflammatory genesis as well as for a treatment of rejection episodes after a transplantation (abstract). However, Ansorge *et al.* do not present data that demonstrate the function and effectiveness of these compounds but rather merely suggest a potential use for the compositions.

18. Andrulis (WO 95/04533 cited on the IDS filed 10/3/2006) teaches methods and pharmaceutical compositions for treating rheumatoid arthritis with thalidomide (abstract), an

alanyl aminopeptidase inhibitor recited in the Markush Group of claims 41-43 of the instant application. Andrulis teaches that thalidomide is also used to treat acute and chronic graft versus host disease (page 2, lines 8 and 9).

19. With the exception of thalidomide, alanyl aminopeptidase inhibitors are not known in the art for upregulating TGF-β or for treating autoimmune and inflammatory conditions.

20. Sharabi *et al.* (*PNAS*, **2006**, *103*, 8810-5) teach that a peptide based on the complementarity-determining region 1 of an autoantibody ameliorates lupus by upregulating TGF-β, suggesting that compounds that increase the level of TGF-β may suppress and treat an autoimmune disease such as lupus.

21. Youn *et al.* (*Clin. Exp. Immunol.*, **2002**, *129*, 232-9) teach that metallothionein, a low molecular weight protein, acts as an immunosuppressant by up-regulating TGF-β and is an effective treatment for collagen-induced arthritis in mice.

(3) the relative skill of those in the art

22. The relative skill of those in the art is high.

(4) the predictability or unpredictability of the art

23. Le *et al.* (*Int. Immunopharm.*, 2005, 5, 1771-82) discuss the unpredictability associated with using TGF-β as a pharmacological agent to treat autoimmune and inflammatory conditions: "TGF-β is an immunoregulatory cytokine. Despite its multiple roles in autoimmune and inflammatory processes, it has been experimentally deployed as a potential therapeutic agent to control autoimmune and chronic inflammatory diseases. TGF-β has been implicated as one of the key regulators of regulatory T cells that are crucial for maintaining balanced immune responses. Nevertheless, its over-production contributes to persistent inflammation, thus

antagonists of TGF-β delivered locally break the cycle of leukocyte recruitment and subsequent fibrosis. On the other hand, systemic administration of TGF-β by injections of the protein or by gene transfer inhibits inflammatory pathogeneses. In addition, enhanced levels of circulating TGF-β appear to be instrumental during the development of oral tolerance and in immunosuppression caused by cyclosporine treatment. The multiplicity of actions of TGF-β and their virtually ubiquitous expression call for more rigorous investigation of their roles in health and disease states and more importantly, careful evaluation of the potential as immunopharmacological agents."

24. Le *et al.* discuss the role of TGF-β in asthma and airway diseases as being particularly unpredictable: "In asthmatic airways, TGF-β1 is an important fibrogenic and immunomodulatory factor that may cause structural changes. Inflammatory cells infiltrating bronchial mucosa, and structural cells of the airway wall including fibroblasts, epithelial, endothelial and smooth muscle cells all of which are TGF-β producers. These diverse cell types increase the levels of TGF-β as observed in bronchoalveolar lavage fluid from asthmatic patients. Elevated TGF-β has been implied in the remodeling of the airway wall, which is related to subepithelial fibrosis. Interestingly, *in vitro* as well as *in vivo* studies have documented dual roles of TGF-β in airway diseases, functioning either as a pro- or an anti-inflammatory cytokine on infiltrating inflammatory cells. These apparently contradictory results may well be the consequences of using different experimental conditions. More clear-cut conclusions concerning the effects of TGF-β may be obtainable from studies using systemic or conditional gene depletion approaches."

(5) the breadth of the claims

25. The claims are drawn to alanyl aminopeptidase inhibitors and inhibitors of all enzymes with a similar substrate specificity. The scope of the enzymes to which the claims pertain is not defined. The scope of potential inhibitor compounds is extremely broad and includes β-amino thiols, α-amino phosphinic acids and their esters and salts, α-amino phosphonats, α-amino boronic acids, α-amino aldehydes, hydroxamates of α-amino acids, N-phenyl phthalimides, N-phenyl homophthalimides, α-ketoamides, thalidomide derivatives, and 3-amino-2-oxo-4-phenylbutanoic acid amides. In addition inhibitor genus includes D-Phe-γ[PO(OH)-CH_2]-Phe-Phe, PAQ-22, RB3014 and MR 387, compounds for which the structures are not disclosed. Finally, the methods for treatment and prevention encompass a broad range of diseases including rheumatoid arthritis, Lupus Erythematodes, multiple sclerosis, insuline dependent diabetes mellitus, Morbus Crohn, Colitis Ulcerosa, psoriasis, neurodermatosis, glomerulonephritis, interstitial nephritis, vasculitis, autoimmune diseases of the thyroid gland, autoimmune-hemolytic anemia or other chronic diseases having an inflammatory genesis, arteriosclerosis, asthma, allergies, hay fever and host versus graft disease.. Each of these conditions have different patient populations, treatments, causes, and symptoms.

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples

26. The specification discloses only that phebestin is capable of increasing the expression of TGF-β1 in and on Treg cells. Given the diversity of chemical structures of the proposed alanyl aminopeptidase inhibitors, the activity of phebestin is not representative of the entire genus. The specification does not include any *in vivo* models for treating or preventing autoimmune

diseases. Thus, the disclosed assays are relevant only to those disease states known in the prior art to be treatable by an upregulation of TGF-β, arthritis and lupus.

27. Furthermore, the specification does not provide structural information on "peptide fragments of pathogenic autoantigens or synthetic analogs and/or specific antigenic components of pathogenic microorganisms" that would be useful for supplementing the alanyl aminopeptidase inhibitors in therapy.

(8) the quantity of experimentation necessary

28. Considering the factors above, the skilled artisan would be burdened with undue experimentation in determining if a compound is an alanyl aminopeptidase inhibitor, if the compound can upregulate TGF-β1 in Treg cells and if the upregulation results in a treatment or prevention of autoimmune and inflammatory condition.

29. Claims 6, 7, 9, 10, 25, 28, and 39-42 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The term "prevention" is interpreted as implying an absolute and complete prevention of the appearance of the disease, i.e., not any overt symptom or pre-symptomatic marker or damage may be present at any level. The specification does not reasonably provide enablement for prevention of autoimmune diseases, allergies, asthma, or hay fever in any species by any means. The skilled artisan cannot envision the prevention of autoimmune diseases, allergies, asthma, or hay fever. For purposes of enablement, the specification must provide reasonable detail in order for those skilled in the art to carry out the invention. The teachings of the specification do not enabled a person of ordinary skill in the art to make and use the claimed method of prevention.

30. Thus, the specification while enabling for the use of phebestin to upregulate TGF-β1 and

to treat lupus and arthritis, does not reasonably provide enablement for all other alanyl aminopeptidase inhibitors or for the treatment and/or prevention of all other autoimmune disorders, hay fever, allergies, asthma or graft versus host disease.

31. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

32. Claims 1-4, 6, 7, 9-11, 17, 20, 25, 28, 30 and 39-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

33. The term "similar" in claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30, and 39-43 is a relative term which renders the claim indefinite. The term "similar" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The use of the term "similar" renders the enzymes which can be inhibited by the claimed compositions and methods indefinite.

34. The phrase "for example" in claim 7 renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

35. Claims 9, 10, and 28 recite the limitation "the type". There is insufficient antecedent basis for this limitation in the claim.

36. Claims 1 and 20 recites the limitation "introduction of the production of TGF-β1 and of the expression of TGF-β1 in and/or on Treg cells." Is introduction of the production the same as expression or is it referring to a process other than expression?

37. Claims 1, 9 and 39 recite the limitation "or of several inhibitors". The use of the word of renders these claims indefinite because it is not clear to what the "of" is referring.

38. Claims 3, 5 and 41-43 recite the limitations "PAQ-2", "RB3014" and "MR 387." Because no structure is disclosed for these chemical names, the claims are vague and indefinite.

Claim Rejections - 35 USC § 102

39. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

40. Claims 20, 25, 28, 30, 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Ansorge *et al.* (WO 01/89569 cited on Information Disclosure Statement received 10/3/2006). Ansorge *et al.* teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, leuhistin, phebestin, amastatin, probestin, β-amino thiols, α-amino phosphinic acids, and α-amino phoshinic acid derivatives (see claim 10). The compositions are disclosed as being useful for the treatment of autoimmune diseases and chronic diseases with an inflammatory genesis as well as for a treatment of rejection episodes after a transplantation (abstract).

41. Regarding claim 20, Ansorge *et al.* does not teach the use of the alanyl aminopeptidase inhibitors for the introduction of the production of TGF-β1 in Treg cells. Regarding claim 28, Ansorge *et al.* does not teach the alanyl aminopeptidase inhibitors for the treatment of allergies or asthma. Because the chemical structure of the species taught by Ansorge *et al.* is identical to the claimed invention, there is a reasonable expectation that the species would meet this additional functional limitation. The discovery and characterization of properties of a known material do not make it novel (see MPEP § 2112). Furthermore, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference (see MPEP § 2112).

42. If the composition is physically the same, it must have the same functional properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) See MPEP § 2112.01. Examiner cannot however determine whether or not the compositions inherently possesses properties which anticipate or render obvious the claimed invention but has basis for shifting the burden of proof to applicant as in In re Fitzgerald, 619 F.2d 67, 205 USPQ 594 (CCPA 1980). See MPEP § 2112.

43. Claims 1, 2, 4, 6, 7, 11, 20, 25, 28, 30, 39-41 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Andrulis (WO 95/04533 cited on the IDS filed 10/3/2006). Andrulis

teaches methods and pharmaceutical compositions for treating rheumatoid arthritis with thalidomide (abstract), an alanyl aminopeptidase inhibitor recited in the Markush Group of claims 41-43 of the instant application. The teaching of Andrulis satisfies all of the limitations of claims 6, 7, 25, 39 and 41. Regarding claims 11, 30 and 42, Andrulis teaches that thalidomide is also used to treat acute and chronic graft versus host disease (page 2, lines 8 and 9).

44. Regarding claim 20, Andrulis does not teach the use of thalidomide for the introduction of the production of TGF-β1 in Terg cells. Regarding claim 28, Andrulis does not teach the use of thalidomide for the treatment of allergies or asthma. Because the chemical structure of the species taught by Andrulis is identical to the claimed invention, there is a reasonable expectation that the species would meet this additional functional limitation. The discovery and characterization of properties of a known material do not make it novel (see MPEP § 2112). Furthermore, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference (see MPEP § 2112).

45. If the composition is physically the same, it must have the same functional properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) See MPEP § 2112.01. Examiner cannot however determine whether or not compositions inherently possesses properties which anticipate or render obvious the claimed invention but has basis for shifting the

burden of proof to applicant as in In re Fitzgerald, 619 F.2d 67, 205 USPQ 594 (CCPA 1980). See MPEP § 2112.

46. Regarding claims 1, 2 and 4, because the compound and method steps are the same as the claimed invention, the effect of administering thalidomide on TGF-β1 production in Treg cells is an inherent result of the method taught by Andrulis.

47. Claims 20, 25, 28, 30 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Ansorge *et al.* (U.S. Publication No. 2004/0147434). Ansorge *et al.* teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, probestin, phebestin, and leuhistin (paragraph 0014). As stated above, the intended use of the claimed compositions is an inherent property of the compositions taught by Ansorge *et al.*

48. Claims 20, 25, 28, 30 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Ansorge *et al.* (U.S. Publication No. 2004/0132639). Ansorge *et al.* teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, probestin, phebestin, and leuhistin (paragraph 0029). As stated above, the intended use of the claimed compositions is an inherent property of the compositions taught by Ansorge *et al.*

49. Claims 20, 25, 28, 30 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Ansorge *et al.* (U.S. Publication No. 2005/0014699). Ansorge *et al.* teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, leuhistin, phebestin, amastatin, probestin, β-amino thiols, α-amino phosphinic acids, and α-amino phoshinic acid derivatives (claim 4). As stated above, the intended use of the claimed compositions is an inherent property of the compositions taught by Ansorge *et al.*

50. Claims 20, 25, 28, 30 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Ansorge *et al.* (U.S. Publication No. 2006/0040850). Ansorge *et al.* teach pharmaceutical compositions comprising the alanyl aminopeptidase inhibitors actinonin, leuhistin, phebestin, amastatin, probestin, β-amino thiols, α-amino phosphinic acids, and α-amino phoshinic acid derivatives (claim 29). As stated above, the intended use of the claimed compositions is an inherent property of the compositions taught by Ansorge *et al.*

51. The applied references for the rejections under 35 U.S.C. 102(e) above have a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Double Patenting

52. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

53. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

54. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

55. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-12 of copending Application No. 10/250,475. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

56. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 33-45 of copending Application No. 10/250,476. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

57. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 10/296,102. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims

7-13 and 20-30 of copending Application No. 10/296,102. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

58. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-22 and 32-42 of copending Application No. 10/507,548. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

59. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 13 and 14 of copending Application No. 10/563,498. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-12 and 15-17 of copending Application No. 10/563,498. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl

aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

60. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 80-87 of copending Application No. 10/575,878. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 78 and 79 of copending Application No. 10/575,878. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

61. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 79-89 of copending Application No. 10/575,882. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 77 and 78 of copending Application No. 10/575,882. Although the conflicting claims are not

identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

62. Claims 1, 2, 4, 6, 7, 9-11, 20, 25, 28, 30 and 39-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 80-86 of copending Application No. 10/575,883. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to methods of administering pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. Claims 20, 25, 28, 30 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 78 and 79 of copending Application No. 10/575,883. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims are drawn to pharmaceutical compositions comprising inhibitors of alanyl aminopeptidase. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

63. No claims are allowed.

64. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Japanese Publication No. 10310599, Japanese Patent No. 410310599A, and U.S. Publication No. 20060040850.

65. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)

272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

66. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

67. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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